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Esthesioneuroblastoma presenting with orbital signs and ectopic adrenocorticotropic hormone syndrome

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ABSTRACT

A 23-year-old woman with known nasal polyps and a recent seizure presented with diplopia, proptosis, extraocular motility deficits, and stigmata of Cushing syndrome. Computed tomography showed a left sinonasal mass extending into the left orbit. Laboratory evaluation revealed refractory hypokalemia and significantly elevated adrenocorticotropic hormone. Histopathologic exam confirmed the diagnosis of esthesioneuroblastoma.

KEYWORDS Esthesioneuroblastoma; neuroesthesioma; olfactory neuroblastoma; sinonasal tumor

Esthesioneuroblastoma, also known as olfactory neuroblastoma, is a rare tumor that arises from the olfactory neuroepithelium.[1] Patients commonly present with nasal congestion or epistaxis; however, extension of this tumor into the orbit can also result in ophthalmic signs and symptoms such as proptosis, diplopia, and epiphora.[2] Some cases may also be associated with paraneoplastic syndromes such as syndrome of inappropriate antidiuretic hormone secretion or ectopic adrenocorticotropic hormone syndrome (EAS).[3] Herein, we present a case of esthesioneuroblastoma manifesting initially with orbital signs and sequelae of EAS.

CASE DESCRIPTION

A 23-year-old woman with known nasal polyps and a recent seizure presented to the emergency department with a 1-month history of binocular diplopia. She also noted unilateral rhinorrhea and weight gain worsening for several months. On examination, there was proptosis of the left eye, incomitant left esotropia, and left-sided adduction and abduction deficits. Nasal exam disclosed a large, gray and flesh-colored mass occluding the left nasal cavity. Hirsutism, central obesity with purple striae, moon facies, and a dorsocervical fat pad were also noted. A computed tomography (CT) scan of the head revealed a 6.4 cm sinonasal mass eroding into the inferonasal left orbit *(Figure 1a)*. The mass abutted the optic nerve without displacing it, and there was displacement of the medial rectus muscle. Magnetic resonance imaging (MRI) of the face demonstrated extensive involvement of the maxillary sinus, nasal cavity, nasopharynx, and nasal vestibule with extension to the left anterior cranial fossa floor *(Figure 1b)*. A biopsy of the mass in the left nasal cavity was performed. During this time the patient required treatment for refractory hypokalemia. An adrenocorticotropic hormone level was obtained and returned >1000 pg/mL (reference range 6–76 pg/mL).

Pathologic interpretation of the biopsied mass returned and showed an epithelioid neoplasm with neuroendocrine differentiation *(Figure 2)*. Immunohistochemical stains revealed tumor cells that were positive for synaptophysin, chromogranin, and CD56. The overall morphologic and immunophenotypic features suggested a diagnosis of olfactory neuroblastoma. Neoadjuvant cisplatin and etoposide were initiated, and the patient was scheduled for outpatient follow-up and eventual resection of the tumor. She returned to the emergency department 2 days later with axillary necrotizing fasciitis and severe sepsis. Unfortunately, her condition worsened despite extensive resuscitation and debridement and she died.

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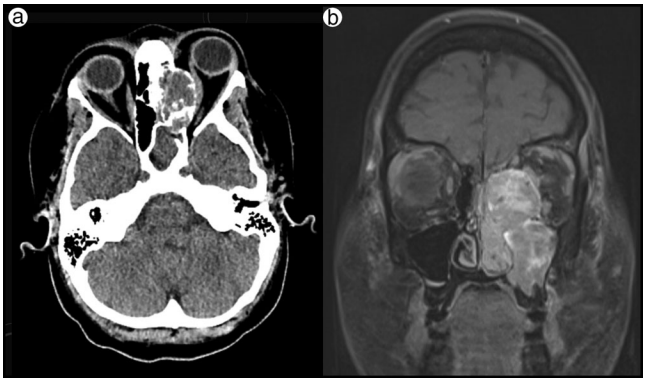

Figure 1. **(a)** CT of the head demonstrating a 6.4 cm sinonasal mass eroding into the inferonasal left orbit with displacement of the medial rectus muscle. **(b)** T1-weighted MRI of the face demonstrating involvement of the maxillary and ethmoid sinuses with extension through the orbit to the left anterior cranial fossa floor.

DISCUSSION

This case represents an extremely rare presentation of esthesioneuroblastoma manifesting with orbital signs and sequelae of EAS. The reported incidence of esthesioneuroblastoma is 0.4 per 1 million people.[4,5] There are conflicting data, as some studies report a bimodal age distribution, whereas others indicate a normal distribution with a peak incidence in the fifth and sixth decades of life.[4,6] Mutations in the sonic hedgehog (Shh) signaling pathway have been associated with development of this tumor; however, there are no reported geographic, environmental, or lifestyle risk factors.[7] Esthesioneuroblastoma is generally a slow-growing tumor that may infiltrate surrounding structures such as the skull base and orbit. There is an association with several paraneoplastic syndromes (syndrome of inappropriate antidiuretic hormone secretion being the most common).[3] EAS has also been reported with this tumor but is extremely rare.[3]

The differential diagnosis for esthesioneuroblastoma includes a wide variety of orbital and sinonasal tumors including cavernous hemangioma, squamous cell carcinoma, sinonasal undifferentiated carcinoma, and inverting papilloma, among others. Diagnosis can prove difficult, as the presenting symptoms are often nonspecific and may mimic more common sinonasal conditions such as rhinosinusitis and nasal polyposis. As a result, there can be an extensive delay between symptom onset and diagnosis.[8] Crucial elements of patient evaluation include tissue biopsy (often possible with nasal endoscopy) and imaging with CT and MRI. Histologic exam of this tumor shows lobules of small, round blue cells occasionally forming Homer-Wright or Flexner-Wintersteiner rosettes.[9]

The diagnosis of esthesioneuroblastoma is most commonly established by positive immunohistochemical staining for synaptophysin and other neuroendocrine markers as well as negative staining for keratin, muscle, melanoma, and lymphoma markers.[3] The Hyams grading system evaluates several adverse histologic features including mitotic activity, nuclear pleomorphism, rosette formation, and architectural

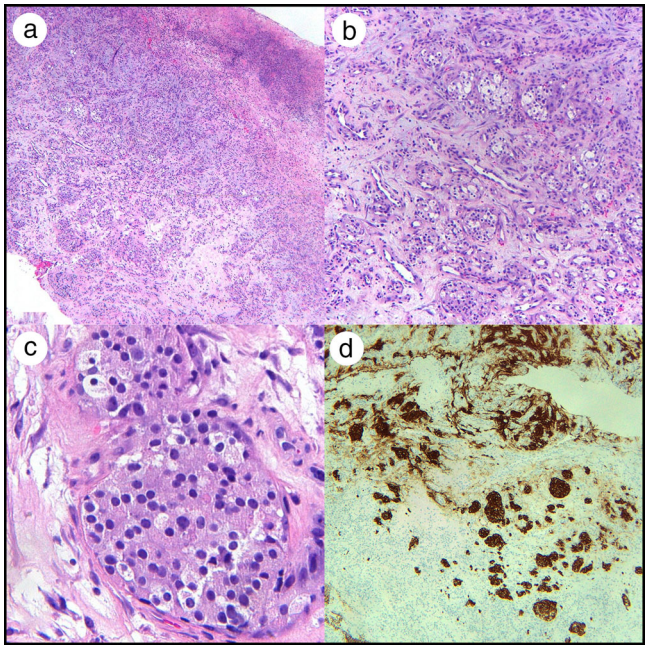

Figure 2. Histopathology with hematoxylin and eosin stain of nasal biopsy specimen under **(a)** low magnification, **(b)** medium magnification, **(c)** high magnification, and **(d)** low magnification with synaptophysin immunohistochemical staining. There are nests of small, round, blue cells with somewhat foamy cytoplasm admixed within granulation tissue.

distortion and assigns a score from 1, more indolent, to 4, more aggressive.[9] The Kadish system is commonly used for staging of esthesioneuroblastoma and assigns a letter for extent of the tumor from A, nasal cavity involvement only, through D, distant metastasis. Although the Kadish staging is used more commonly as a prognostic indicator, some studies suggest that the Hyams grade at presentation is more predictive of patient outcomes.[4]

Treatment most often involves a multidisciplinary effort between otolaryngology, medical oncology, radiation oncology, and ophthalmology if there is intraorbital extension of the tumor. Due to the nonspecific symptoms early in the disease course, most patients do not present until higher Kadish stages.[4] Resection followed by radiotherapy is the standard of care at most institutions.[10] The efficacy of neoadjuvant or adjuvant chemotherapy for esthesioneuroblastoma remains controversial; however, a combination of cisplatin and etoposide is the most commonly used regimen.[11] Prognosis is related to Kadish staging and Hyam grading, as Hyam 4 and Kadish D tumors demonstrate the worst outcomes.[12]

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